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ELI LILLY AND COMPANY

By Linda M. Durbin Date January 8, 2004

PATENT APPLICATION
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Janet M. Hock et al.	
Serial No.	:	09/647,278	
Filed	:	September 26, 2000	Group Art Unit: 1646
For	:	Method of Increasing Bone Toughness and Stiffness and Reducing Fractures	Examiner R. Li
Docket No.	:	X-11965	

COMMUNICATION

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450
Sir:

Applicants submit this Communication following a personal interview between Applicants' attorney and the Examiner and his Supervisor, on December 16, 2003.

Applicants cite herewith additional documents for consideration by the Examiner.

Remarks

Applicants continue to maintain the arguments of record that Neer cannot be a basis for anticipation of the claimed invention, and that, in the absence of the PTH standard stipulated by Neer, it was improper to import specific activity information from the prior art in order to convert Neer's dosage from units to micrograms. The arguments

presented in the Preliminary Amendment, filed October 29, 2003, and in all previous responses are reiterated. Applicants maintain that the present rejection is improper and lacking in the legal requirements for an anticipation.

Anticipation Cannot be Based on Mere Possibility

The standard for anticipation is quite high. The law requires that a single prior art reference expressly or inherently teach the claimed invention. Uncertainty or ambiguity as to what is taught by an allegedly anticipatory reference eviscerates any basis for an anticipation argument.

In *Ex parte Standish*, the Board of Patent Appeals overturned a rejection under Section 102 based on conjecture as to what was taught by an allegedly anticipatory reference. In *Standish*, the Examiner rejected claims to an audible fishing lure for anticipation, principally based on the examiner's interpretation that a figure in a prior art reference may have disclosed a key element of the claimed invention. The Board held, "anticipation of a claimed product cannot be predicated on mere conjecture as to the characteristics of a prior art product." *Ex parte Standish*, 10 USPQ2d 1454 (BPAI 1988).

The pending rejection rests on speculative and uncertain results. The Examiner imported specific activity values from the prior art in order to convert Neer's dosage from units to micrograms. Table 1 displays the results achieved by the Examiner, as well as other results achieved by application of selected references cited in Applicants' IDS.

Table 1.

Reference	**IDS Reference Code**	**Specific Activity (units/ug)**	**Conversion of Neer's 100-700 units to microgram**
Finkelstein (1994)	CAH	12.5	8 ug - 56 ug
Fujita (1999)	CL	3.3	30 ug - 212 ug
Hodsman (1997)	CN	15	6.7 ug - 46.6 ug
Lane (1998)	CE	16	6.2 ug - 43.8 ug

Reeve (1980)	CO	7.5	13.3 ug - 93.3 ug
Reeve (1987)	CU	10	10 ug - 70 ug
Sone (1995)	CAA	3	33.3 ug - 233.3 ug

Clearly, importation of specific activity values from the prior art to interpret Neer yields broadly divergent results that are anything but certain. The reason for this uncertainty is clear: the prior art provides specific activity values for hPTH(1-34) that are broadly dispersed, from a low of 1 U/ug to a high of 16 U/ug (*cf.* Tables 1 & 2).

The uncertainty that is manifest from these results reveals the untenability of the rejection. An allegedly anticipatory reference *must* teach *each element* of the claimed invention, either expressly or inherently. Anticipation cannot rest on mere speculation or guesswork about the teachings, or the possible interpretation, of a reference. A finding of anticipation rests on that which is certain and necessarily taught by the reference. The pending rejection fails to achieve this standard.

Apparently the Examiner disagrees. The rejection asserts on Page 7 (Paper 14) that the published specific activity values of PTH(1-34) are "quite close to each other and quite consistent." As Tables 1 & 2 clearly show, however, the cited references demonstrate a sixteen-fold variance from lowest to highest published specific activity values for PTH(1-34). The same degree of ambiguity and uncertainty is transferred to Neer upon conversion, thereby undermining any argument as to what Neer *necessarily* teaches.

In spite of this uncertainty, the Examiner chose two specific activity values from the prior art (i.e. 16 U/ug and 12.5 U/ug) that were applied to Neer to generate ranges that overlap with Applicants' claimed 20 ug dose (i.e. 6-44 ug and 8-56 ug, respectively).

The rejection provides no justification for choosing these *particular* specific activity values, as opposed to other

values. For example, if Sone's specific activity (3 U/µg; IDS reference CAA) is applied, a range of 33.3 - 233.3 µg results for Neer. If Fujita's specific activity (3.3 U/ug; IDS reference CL) is applied, a range of 30 - 212 ug results for Neer. Under these conversions, Applicants' claimed dose of 20 µg/day clearly falls outside the scope of Neer.

Additional documents disclosing PTH standards

Following a personal interview between Applicants' attorney and the Examiner and his Supervisor on December 16, 2003, and pursuant to the Examiners' suggestion, Applicants cite herein additional documents that disclose PTH standards.

Table 2 lists several documents that disclose various PTH standards. Two of the standards are from human sources while the third is from a bovine source. None of these standards appears to correspond with the standard specified by Neer, namely the "International Reference Preparation of hPTHF 1-34" (Col 5, lines 4-5).

Table 2

Reference (IDS Code)	Date Available	PTH Standard	Sp. Activity	WHO/NIBSC Code
CAO; CAP	1983	First International Reference Preparation (Human PTH)	1 U/ug	79/500
CAO	1985	First International Standard (Bovine PTH)	2.5 U/ug	82/632
CAQ; CAR	Nov. 1985	Research Standard (Human PTH 1-34)	8.8 U/ug	82/508

One of the human standards - the "First International Reference Preparation for Human PTH," (Code 79/500) provides a human PTH standard having a specific activity of 1 Unit/ug. Application of the 79/500 standard specific activity to Neer results in a conversion of Neer's 100-700 units to 100-700 ug, again outside the scope of Applicants' claimed invention.

A second standard - designated the "First

International Standard, Bovine PTH" (Code 82/632), comprises bovine PTH having a specific activity of 2.5 units/ug. Application of the specific activity for the 82/632 standard to convert Neer, results in a dosage range of 40 ug-280 ug, again outside the scope of Applicants' claimed invention.

The third standard (Code 82/508), comprising human PTH(1-34), does *not* constitute an International Reference Standard, or International Reference Preparation. Instead, the 82/508 material is provided as a "Research Standard". This material was characterized in 1985 as moderately pure (85-90%)(IDS Reference CAR). The 82/508 reagent has never been sanctioned as an International Reference Standard or International Reference Preparation and should not be regarded as such[1].

Applicants request withdrawal of the rejection and passage of the case to issuance as soon as possible.

Non-obviousness of the Claimed Invention

The pending rejection rests solely on alleged lack of novelty over Neer. In the interest of expediting prosecution, Applicants provide herein additional argument in support of the non-obviousness of the claimed invention.

Applicants' claims are directed at the administration of a specific dose of PTH(1-34) - namely 20 ug/day, to reduce the risk of bone fracture in osteoporosis patients. The prior art, including Neer, fails to teach, or suggest the claimed invention.

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[1] The designation "International Standard" conveys a specific meaning to the skilled artisan, denoting authorization by an international sanctioning body. Specifically, "International Reference Preparation" and "International Reference Standard" mean that the standard has been sanctioned by the World Health Organization (WHO) and/or NIBSC after rigorous testing and characterization by an international cadre of research labs.

Prima facie obviousness requires a showing that: 1) the claimed invention was suggested by the cited art, and 2) the cited art, alone or in combination, provides a likelihood of success in achieving the claimed invention. *In re Dow Chemical Co.*, 5 USPQ2d 1529 (Fed. Cir. 1988). Neither of these requirements are fulfilled in the present case.

No suggestion of claimed dose

Applicants claim the administration of 20 ug/day of PTH(1-34) to reduce the risk of bone fracture in osteoporosis patients. References of record teach administration of PTH(1-34) at doses higher than claimed by Applicants, for the purpose of increasing BMD. No reference to which Applicants are aware, teaches or suggests Applicants' claimed invention.

As already stated, Neer absolutely fails to disclose the *claimed* administration of PTH(1-34) at a specific dose of 20 ug/day without concurrent administration of an antiresorptive agent (other than calcium and/or vitamin D). Other references of record disclose dosages of PTH(1-34) that are from 2 to 5-fold higher than Applicants' claimed dose, i.e. from 50 ug to 100 ug/day (*See e.g.* IDS references CO, CZ, CU, CN), and/or combination or cyclical regimens in which PTH is co-administered with an antiresorptive agent, such as estrogen or calcitonin (*See e.g.* Lindsay et al; IDS Reference CB).

No suggestion of reduced fracture

Applicants' discovery that exogenously administered PTH reduces the risk of bone fracture in osteoporosis patients is highly significant. While the prior art taught administration of PTH(1-34) to increase bone mass, the art did not teach or suggest administration of PTH for reducing the risk of bone fracture.

A priori it might seem reasonable to suppose

that an increase in BMD or bone mass would presage a reduction in bone fracture. However, this is not the case. The clinical experience has proven that increases in BMD and/or bone mass do not necessarily correlate with reduced fracture. For example, it is now known that compounds such as fluoride, which increase BMD quite substantially, have little or no affect - and in some cases a negative affect - on the incidence of bone fracture. On this point, Riggs states, "increased bone mass induced by treatment [i.e. with fluoride] does not necessarily correlate with increased bone strength . . . Moreover . . . fluoride therapy significantly *increased* the rate of both incomplete and complete non-vertebral fracture." Riggs, *A. J. Med.* 91, 5B-39S.

In a similar vein, Hodsman stated in 1998 that there was uncertainty as to whether PTH treatment would have a beneficial effect on fracture rate:

> The controversial studies of the use of sodium fluoride and bisphosphonates have not universally supported the assumption that increased bone mass . . . reduces fracture risk. Nor are there definitive studies that indicate whether increases in bone mass induced by PTH will translate into a reduced fracture risk. Hodsman et al. In *Parathyroid Hormone: the Clinical Experience & Prospects*, CRC Press 1998, pp 83-108 (emphasis added).

Thus, prior to Applicants' disclosure, the art failed to teach or suggest that administration of PTH would reduce the risk of bone fracture.

To follow further on this point, there were other reasons that are apparent in the prior art that clearly teach away from Applicants' claimed invention. According to the prior art, the gains realized in vertebral BMD following administration of PTH were at the expense of loss in BMD in

cortical bone.[2] This bone-leaching phenomenon came to be known as "robbing Peter to pay Paul." The "robbing Peter" effect led to the fear that PTH could not be administered alone without subjecting patients to increased risk of fracture at non-vertebral sites, primarily the hip. This led many researchers to advocate use of PTH in combination with a bone antiresorptive agent, such as estrogen or calcitonin, in order to mitigate the negative impact on non-vertebral bone.

With this knowledge background provided in the prior art, it was surprising and unexpected that PTH, an agent known to increase bone resorption and reduce BMD at non-vertebral sites, would be effective in reducing the risk of bone fracture at all sites when administered without an antiresorptive agent. Applicants assert the claimed invention was not taught or suggested by the prior art. If anything, the prior art taught away from the claimed invention.

Applicants assert they have answered all bases of the rejection, and respectfully request withdrawal of the rejection and passage of the case to issuance as soon as possible.

Respectfully submitted,

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[2] See IDS references CO, CP, CQ, CR, CS, CT, CV, CX, CZ, and CAF.